

# A Drug Is not an Outcome: Extending Translation Through Implementation Using Real-World Data

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**Our quest for impact requires us to extend the translational vision and drive innovation not only from lab to clinical study but from trial patients to real-world populations. Closing this implementation gap requires imaginative research, robust real-world data, and an impassioned cadre of champions—patients, regulators, front-line practitioners—keen to see the promise of basic science and the labors of translational research find effective, consistent expression in the practice of medicine.**

“A gene sequence is not a drug,” physician-scientists Goldstein and Brown reminded readers in their classic 1997 essay<sup>1</sup> lamenting the excessive focus of medical science on reductive approaches. Successful therapeutic development, they argued, required not only a cadre of basic and disease-oriented laboratory researchers but also patient-oriented investigators, “the clinical scholar with the analytical insight to point biotechnology companies towards the Achilles heel of a stubborn disease.” Such investigators, contended the authors, represent the “rate-limiting factor” in “the development of approved products.”

Reflecting on these observations two decades later, it's difficult not to be struck by their prescience, anticipating the renewed emphasis on patient-centricity in medical and pharmaceutical research. But it's equally clear that this patient-focused vision of translation may not have been ambitious enough. After all, our collective goal isn't a scientific paper, a candidate molecule, a successful randomized control study, or even a US Food and Drug Administration (FDA)-endorsed drug; rather, it's the diffusion of promising, well-validated technology into the broader population, where its impact

can be rigorously evaluated and progressively optimized. Just as a gene sequence is not a drug, a drug is not an outcome.

## BEYOND THE TRANSLATIONAL GAP

The progressive recognition that basic research doesn't translate effortlessly into novel therapeutics resulted in a closer look at the “translational gap,” and a focus on how to cross the so-called “valley of death” between laboratory science and a clinical product. Several attempts to measure the gap between bench and bedside have suggested an average delay of 17 years, although this figure is based on relatively limited data and conceals exceptional heterogeneity;<sup>2</sup> even more concerning, however, is that the terminal event in most studies of translation is at best the incorporation of a new technology into professional practice guidelines, taken as a sign of community acceptance. As Morris *et al.* point out, “the gap between guideline publication and translation into actual practice is often ignored.” Remarkably, the process measures typically used in the assessment of translational efficiency rarely assess the one we arguably should care most about: the impact of validated new technology on all eligible patients.

What we really would like, and need, is to assess the breadth and speed of innovation diffusion and to understand how well a new innovation is actually working—are the results obtained in the promising pivotal clinical trials, for example, bearing out in the real world? What are the patient factors, the provider factors, the community and environmental factors associated with real-world performance of a new technology? For whom is the promise not being realized? Are there examples where the benefit is greater than expected, perhaps because of refinements suggested by an inquisitive physician or an imaginative patient?

To address these questions around the diffusion of innovation, real-world data (RWD)—routinely collected health data—and real-world evidence (RWE)—clinical evidence, derived from RWD, related to a medical product—is required.

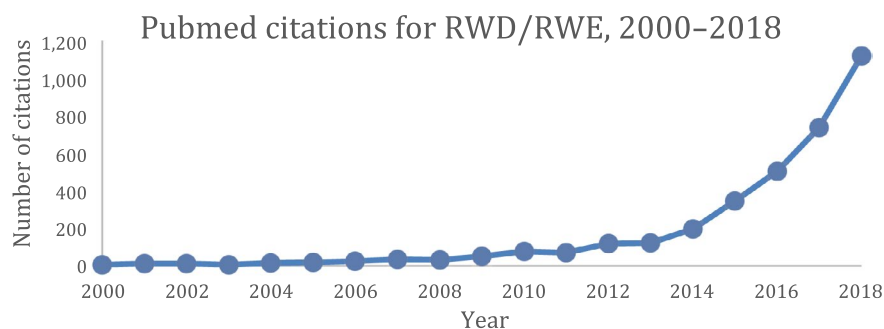
## RWD

As suggested by citations in PubMed (**Figure 1**), there is rapidly growing interest in RWD and RWE, motivated by a range of considerations, including an appreciation for the limitations of traditional randomized controlled trials (RCTs): patients encountered in typical practice settings tend to be older, sicker, more complex, and less adherent than those evaluated in most pivotal trials.<sup>3</sup> The digitalization of medical information has also prompted many to ask whether this extensive trove of information could be productively mined to explore questions historically evaluable only through traditional RCTs. And there are some cases where the disease is so rare, or the course so consistently grave, that a traditional RCT can seem either unfeasible or unethical.

The FDA has recently released a framework seeking to increase use of RWE “to explore the potential for using RWE to help support approval of new indications for approved drugs or to support or satisfy post-approval study requirements.”<sup>4</sup>

But as useful as RWE may be in supporting the regulatory review of emerging technologies, the most impactful application of RWE may be in delineating the region between approval and adoption—the implementation gap.

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**Figure 1** Citations for “real-world data” or “real-world evidence” in PubMed from 2000 through 2018. RWD, real-world data; RWE, real-world evidence.

Following FDA approval, most medical innovations are released into the wild with relatively minimal follow-up assessment to determine how well their performance in populations matches up with the promise demonstrated in the pivotal trials. But ultimately, it’s the real-world performance that we care most about and that, ideally, we seek to optimize.

Research into real-world use of approved technologies is likely to identify instances where implementation is falling short—for example, epidermal growth factor receptor testing in Medicare patients<sup>5</sup>—and where it seems to have occurred with great rapidity, such as adoption of noninvasive prenatal testing for the evaluation of common trisomies in pregnant women and the use of programmed death-ligand 1 testing by community oncologists.<sup>6</sup>

### INVENTION VS. IMPLEMENTATION

The broader idea is that RWE offers a guide to the diffusion of technology and provides a tool to define the gaps between theoretic and achieved results, surfacing, and in many cases even quantifying, obstacles. Revealing these gaps points future innovators at these opportunities, gives them a target to hit, and reminds stakeholders of the real-world needs experienced by patients. It’s easy to forget that an approved drug for an indication doesn’t mean it’s being used by patients or embraced by physicians—perhaps out of ignorance, perhaps for good reason. Frontline physicians are likely to have unique insight into the real-world challenges associated with a new technology and may be uniquely positioned to propose solutions.

We are often tempted to frame new technology in what James Bessen<sup>7</sup> has described

as the “Great Inventor” narrative, celebrating the person “who brought wondrous inventions and wealth to the ignorant masses.” But the reality is that technology rarely arrives on the scene fully formed—more often it is rough-hewn and finicky, offering attractive but elusive potential. As Bessen has observed, “invention is not implementation,” and it can take decades to work out how best to use something novel. “Major new technologies typically go through long periods of sequential innovation,” Bessen observes, adding, “Often the person who originally conceived a general invention idea is forgotten.”

Economic historian Robert Gordon echoes this point in his epic treatise on American growth, noting in the case of transportation innovations, “most of the benefits to individuals came not within a decade of the initial innovation, but over subsequent decades as subsidiary and complementary sub-inventions and incremental improvements became manifest.”<sup>8</sup>

In areas ranging from the power loom where efficiency improved by a factor of twenty, to petroleum refinement, to the generation of energy from coal, remarkable improvements occurred during the often lengthy process of implementation, as motivated users figured out how to do things better, “learning by doing” as Bessen describes it in his book of the same name.<sup>7</sup>

Many of these improvements are driven by what Massachusetts Institute of Technology professor Eric von Hippel calls “field discovery,” involving frontline innovators motivated by a specific, practical problem they’re trying to solve. Such innovative users—the sort of people who Judah Folkman had labeled “inquisitive physicians”—play a critical role in discovering

and refining new products, including in medicine; a 2006 study led by von Hippel of new (off-label) applications for approved new molecular entities revealed that nearly 60% were originally discovered by practicing clinicians.<sup>9</sup>

### GETTING THERE

Given the importance of implementation, what can be done to prioritize its pursuit? First, and perhaps most importantly, we must identify implementation as a critically important objective for medical research. Second, we should recognize the importance of practitioners, of von Hippel’s “lead users,” including both the providers in the trenches as well as the patients in their care; these patients and caregivers are not only the focus of implementation efforts but are partners in discovery<sup>10</sup> and often the most impassioned and effective innovators in implementation. Third, we need timely, high-quality RWD, in a comprehensive fashion—a pragmatic challenge for contemporary researchers even when such data are available, given the structure of typical data-use agreements, which tend to explicitly prohibit data aggregation.

Imagine, for a moment, if the data available from clinical practice were consistently on par with that of clinical trials, and if safety and efficacy—the two criteria driving FDA approvals—could be assessed reliably in the real-world setting. While not obviating the need for RCTs, such “regulatory-grade” RWD would enable the consideration of a refined approach to regulation more comfortable with bestowing provisional, earlier approvals because of the concomitant opportunity (and responsibility) to evaluate robustly whether the promised performance was being realized and to reconsider products that in broader clinical practice were failing to live up to these expectations. Such regulatory focus on real-world performance—assessed and updated continuously—would place appropriate pressure on innovators to better understand and more effectively address the factors associated with successful implementation.

### CONCLUSION

The gap between FDA endorsement of a new technology and the successful implementation of this technology in the broader population (including, potentially,

the recognition that a new technology isn't broadly useful) has largely remained hidden from view; the challenge of moving science from the lab into the clinic would seem to be difficult enough. But our quest for impact requires us to extend the translational vision. We must not only drive innovation from lab to clinical study but then push it even further, from carefully selected trial patients to real-world populations, an implementation gap that requires imaginative research, rigorously collected RWD, and an impassioned cadre of champions, including patients, regulators, and front-line practitioners who are keen to see the promise of basic science and the labors of translational research find effective, consistent expression in the practice of medicine.

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# Information Patients Can Provide Will Strengthen the Real-World Evidence That Matters to Them

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**Despite traditional reliance on data from claims and electronic health records (EHRs) for real-world evidence (RWE), health stakeholders acknowledge that patients are in a position to provide key information that complements existing product performance data. The potential of patient-generated data to improve health outcomes and drive innovation has not been fully realized. Its value comes from both the information itself and the opportunity to engage patients in creating RWE in ways that may benefit patients and all stakeholders.**

#### COMMENTARY

Patients regularly grapple with making complex decisions about their treatment in an environment where provider appointments are brief and there is limited opportunity to discuss disease management preferences and goals. Studies show that patients are capable of understanding and ranking their treatment preferences,<sup>1</sup> but whether they have enough practical data to inform those choices is a central question. Patients want to know which treatment or device works best for them and to hear what their peers have experienced with a product or procedure they are considering. From a patient-centered perspective, RWE is essential, revealing aspects of a medical product that would be impossible to show via randomized controlled trial. A typical patient often manages comorbid conditions or other unique characteristics that would preclude them from randomized controlled trials, but these are precisely the patients

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